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TOBACCO AND BLADDER CANCER IN MALES: INCREASED RISK FOR INHALERS AND SMOKERS OF BLACK TOBACCO

J. CLAVEL[1], S. CORDIER[1], L. BOCCON-GIBOD[2] and D. HEMON[1]

[1]*Institut National de la Santé et de la Recherche Médicale, Unité 170, Villejuif; and* [2]*Service d'Urologie, Hôpital Bichat, Paris, France.*

Relationships between risk of bladder cancer and tobacco smoking were assessed from a hospital-based case-control study conducted in France from 1984 to 1987. Smoking history was analyzed for 954 male patients (477 cases and 477 controls). The odds ratio (OR) of bladder cancer was estimated at 3.95 for all smokers *vs.* non-smokers. The risk increased with duration of smoking and with average daily cigarette consumption, but there was a significant interaction between these 2 parameters, since the risk only increased with average daily consumption when the duration exceeded 20 years. Black tobacco consumption and inhaling were both found to double the risk when analyzed separately, but their respective effects appeared to interact, and an elevated risk for smokers of black tobacco was only observed among inhalers. Smokers of black and blond tobacco also differed in the way in which the risk evolved with time after cessation of smoking. The OR decreased faster after cessation of smoking among smokers of black tobacco than among smokers of blond tobacco, but the residual risk was higher 15 years after cessation among the former than among the latter.

There is strong evidence that smoking increases the risk of bladder cancer. In most published surveys, the relative risk for smokers compared to non-smokers was about 2, with variations from 1 to 5 depending on the country. Vineis *et al.* (1984) have suggested that these discrepancies might correspond to differences in the type of tobacco smoked, since the risk appears to be higher in Latin countries where the use of air-cured (*i.e.*, black) tobacco is more common. An excess risk has indeed been found for smokers of black tobacco in the 2 studies in which this type of analysis has been performed (Vineis *et al.*, 1984; Iscovich *et al.*, 1987).

With regard to inhalation, available data remain conflicting. The relative risk for inhalers *vs.* non-inhalers is about 2 in France (Schwartz *et al.*, 1961), and about 1.5 in the USA (Cole *et al.*, 1971; Morrison *et al.*, 1984; Slattery *et al.*, 1988) and in Japan (Morrison *et al.*, 1984). In 3 other studies, inhalation was not observed to have any relationship with the risk of bladder cancer (Hartge *et al.*, 1987, in the USA; Howe *et al.*, 1980, in Canada; Morrison *et al.*, 1984, in the UK). On the other hand, both Hartge *et al.* and Howe *et al.* observed an increased relative risk for inhaling *vs.* non-inhaling pipe smokers.

Both inhaling and the type of tobacco smoked appear to modify smoke constituents, especially some nitrogen compounds which are known to be bladder carcinogens (Hicks, 1980; IARC, 1986). In particular, the concentrations of N-nitrosamines and 2-naphthylamine are higher in black than in blond tobacco smoke. Furthermore, N-nitrosamine formation from nicotine is not only exogenous but also endogenous, and endogenous formation is increased by inhaling (Hoffmann *et al.*, 1984; IARC, 1986). Experimental data have provided some evidence that urinary mutagenicity might be higher for smokers of black than of blond tobacco (Hoffmann *et al.*, 1984; IARC, 1986; Mohtashamipur *et al.*, 1987; Malaveille *et al.*, 1989). Bryant *et al.* (1988) also showed a higher level of 4-aminobiphenyl hemoglobin adducts among smokers of black than of blond tobacco.

It therefore appeared of great interest to investigate smoking histories, with special reference to inhalation and to the type of tobacco smoked. As the nature of exposure to carcinogens seems to differ according to these smoking habits, we attempted to consider the time-related variations in their effect on the risk of bladder cancer, in light of the multi-stage models of carcinogenesis (Chu, 1987; Breslow and Day, 1987).

MATERIAL AND METHODS

The present study is part of a hospital-based case-control survey on occupational risk factors of bladder cancer for men and women, carried out in 7 French centers between 1984 and 1987.

Cases and controls

Cases were males under 80 years of age, for whom the diagnosis of bladder cancer had been histologically confirmed. Cases were recruited during the whole study period. The only systematic reason for not interviewing was related to interviewer schedules (*i.e.*, replacement of interviewers, holidays). In all, 477 cases were included in our study; 320 of them had been diagnosed less than 1 year before interview.

For each case, one male control was randomly selected in the same hospital, and matched with a case for age (±5 years), residence and ethnic group. Patients admitted for respiratory disease or cancer were not included as controls, because of the possible association between these diseases and occupational exposure. Furthermore, case and control pairs in whom the control had been admitted for vascular or ischemic heart diseases were excluded from specific analysis, because these diseases are strongly related to tobacco consumption. No patients with hematuria or other possible symptoms suggestive of bladder cancer were included as controls.

Interview

Cases and controls were interviewed according to a standard questionnaire, which included questions about demographic characteristics, diet, drug consumption and life-long occupational history. Detailed information about smoking habits was collected for cigar, pipe and cigarette consumption. For each brand of tobacco the patients smoked, they were asked to specify their age at the beginning and end of the period concerned, usual daily consumption and (for cigarette smokers) whether they used filter tips. Lastly, smokers were asked if they inhaled habitually, sometimes, or not at all.

Definition of tobacco-related variables

Smokers included every patient who had ever smoked, regardless of quantity and duration. They were classified as former smokers when they had stopped smoking 2 years or more before diagnosis, and otherwise as current smokers. The "age at diagnosis" of each control was taken as the age at diagnosis of the corresponding cancer case. Smoking history was studied from the age at which smoking started up to the age at diagnosis. The amount smoked was expressed in terms of *average daily consumption.* Cigarette tobacco brands were

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TABLE I – DISEASES DIAGNOSED IN CONTROLS AT HOSPITALIZATION

	n	%
Osteoarticular diseases	143	30.0
Digestive diseases (ulcers:16)	125	26.2
Non-ischemic heart diseases	64	13.4
Ill-defined symptoms and morbid states	36	7.5
Traumatisms	26	5.4
Nervous system diseases	19	4.0
Nutrition and endocrine diseases	15	3.1
Genito-urinary diseases	14	2.1
Others	35	7.3
	477	100

classified as blond or black on the basis of information provided by the French state monopoly of cigarette manufacture (SEITA). The *type of tobacco* smoked was then defined from the total life-long consumption as black (*i.e.*, 90% of black tobacco or more), blond (10% of black tobacco or less), or mixed. A few brands remained unclassified. The *use of filter cigarettes* was quantified as the proportion smoked during the total life-long consumption. Subjects who said they inhaled smoke, even occasionally, were classified as *inhalers*.

With regard to *time-related variables*, age at starting, total duration of cigarette consumption, and time since cessation were considered.

Analysis

Odds ratios were estimated by unconditional logistic regression adjusted for age, hospital and residence, using BMDP®. Models were compared by the Maximum Likelihood Ratio test. Conditional logistic regression was performed using Epilog®.

RESULTS

Distributions of age, residence and ethnic group (97.5% of the subjects studied were European) were similar for cases and controls. No significant difference between the groups was found for social class, as defined by the last employment. Mean age was 62.3 years for cases and 61.5 years for controls. The diseases diagnosed in controls at admission are listed in Table I.

Analysis of main effects of tobacco-related parameters

Table II gives the ORs, adjusted for matching variables associated with different parameters of tobacco consumption. Only 4 cases and 20 controls exclusively smoked cigars or a pipe; and were therefore excluded from further analysis of cigarette smoking. After adjustment for matching variables (*i.e.*, age, hospital and residence), the ORs were 3.95 for cigarette smokers *vs.* non-smokers, and 5.14 and 2.96 respectively for current and former smokers *vs.* non-smokers.

The relationships between bladder cancer on the one hand and average daily cigarette consumption, inhaling, or type of tobacco, on the other, were highly significant and persisted after the exclusion of non-smokers. The increase in the odds ratio with average daily consumption did not depart significantly from linearity. The use of filter tips did not appear to be

TABLE II – ESTIMATED ODDS RATIOS[1] FOR BLADDER CANCER ACCORDING TO VARIOUS TOBACCO-RELATED PARAMETERS (EXCEPT FOR SMOKING STATUS, CIGAR OR PIPE SMOKERS WERE EXCLUDED FROM THE ANALYSIS)

	Cases	Controls	OR	CI (95%)[3]	*p*-value[2]
Smoking status					
Non-smokers	35	104	1.00		***
Cigar or pipe smokers	4	20	0.59	[0.19–1.86]	
Cigarette smokers	438	353	3.95	[2.61–5.99]	
Current cigarette smokers	259	171	5.14	[3.30–8.00]	
Former cigarette smokers	179	182	2.96	[1.89–4.63]	
Total	477	477			
Average daily consumption (number of cigarettes per day)					
Non-smokers	35	104	1.00		***
1–19	200	191	3.26	[2.10–5.08]	
20–39	186	137	4.41	[2.81–6.92]	(**)
>40	52	25	6.92	[3.71–12.91]	
Total	473	457			
Inhaling					
Non-smokers	35	104	1.00		***
Non-inhalers	114	164	2.12	[1.33–3.36]	
Inhalers	324	189	5.67	[3.67–8.75]	(***)
Total	473	457			
Type of tobacco					
Non-smokers	35	104	1.00		***
Blond	24	40	1.89	[1.24–2.88]	
Mixed	30	33	2.96	[1.57–5.69]	(**)
Black	353	252	4.37	[2.30–8.30]	
Unknown	31	28			
Total	473	457			
Percentage of filter-tip cigarettes (% of total life-long consumption)					
Non-smokers	35	104	1.00		***
<50	300	231	4.03	[2.63–6.17]	
50–75	19	13	4.77	[2.10–10.82]	(NS)[4]
75–99	27	19	5.03	[2.45–10.35]	
100	65	71	3.14	[1.86–5.30]	
Unknown	27	19			
Total	473	457			

[1]OR: odds ratios estimated by logistic regression including matching variables: hospital, age and residence.–[2]*p*-value: significance of likelihood ratio χ^2 test; in brackets: significance of likelihood ratio χ^2 after exclusion of non-smokers.–[3]CI (95%): 95% confidence interval for OR.–[4]NS: Not significant; $^{**}p < 0.01$; $^{***}p < 0.001$.

associated with a statistically significant decrease in the bladder cancer risk.

Table III gives the ORs according to time-related variables, adjusted for matching variables. The OR increased with the total duration of cigarette consumption and reached a plateau after 30 years. It was higher when age at beginning to smoke was low. In former smokers, it decreased regularly with time after the cessation of cigarette consumption.

Multivariate analysis

We began the analysis by testing each order-2 interaction separately, and searching for possible confounders among the smoking variables. Next, we performed a backward stepwise logistic regression so as to delete non-significant terms and non-confounders.

Studies of the interactions and relations between smoking variables were restricted to smokers, to avoid using the same unexposed non-smoker class for analysis of all the parameters.

The following order-2 interactions were significant: duration × average daily consumption, type of tobacco × inhaling, and time since cessation × inhaling and × type of tobacco. These were included in the complete model of stepwise logistic regression, and will be described later.

Relationships between tobacco-related variables were studied among controls. The proportion of inhalers among smokers was significantly higher when age at beginning to smoke was lower, the duration of smoking longer, and to a lesser extent, average daily consumption higher. Furthermore, the proportion of inhalers was greater when time since cessation was short. As expected, smokers of black tobacco used filter tips less frequently than those of blond tobacco, and had smoked for longer periods of time. These findings are consistent with the fact that only a few brands of French cigarettes, mostly consisting of black tobacco, have filter tips and that blond cigarettes which usually have filter tips are imported and have mainly been consumed only in recent years. There was no statistically significant relationship between the use of filters and inhaling, or between the type of tobacco smoked and inhaling.

The study of time-related variables was difficult because each variable is a linear combination of the others. The latency period is the difference between age at diagnosis and age at the start of cigarette consumption, and is also the sum of the total duration of smoking and time since cessation. Because of these colinearities, it was impossible to study the time-related variables simultaneously, since age was a fixed parameter. One possibility would have been, like Hartge *et al.* (1987), to perform a separate study of smokers who had suspended their consumption for a certain time, but only a few smokers in the present study had done so. An additional difficulty in our study lay in the fact that the effects of age at beginning and of inhaling were confounded. For these reasons, further details on age at beginning will not be informative.

Because of numerous connections between tobacco-related variables, inclusion of confounding and interacting factors in the analysis of all effects of interest required inclusion in the minimum logistic model of all first-order terms, the 4 significant interaction terms, and the 3 matching variables. As shown in Table IV, age at start of smoking, use of filter tips, and one interaction term, (time since cessation) × (inhaling), were excluded from this model by backward logistic regression.

As regards the effects of the 3 remaining interaction terms, their observed age-adjusted odds ratios were considered separately.

The relationship between average daily consumption and bladder cancer risk was not statistically significant in the subgroups of patients who had smoked for less than 20 yr (Table VA and Fig. 1). A rise in the OR for smokers of black *vs.* blond tobacco was only observed among inhalers (Table VB and Fig. 2). After cessation of smoking, the evolutive pattern depended on the type of tobacco smoked: thus, among smokers of black tobacco, the OR decreased immediately after cessation, and by 15 years thereafter it had dropped to about half the level observed at cessation. In contrast, among smokers of blond tobacco, the odds ratio rose for about 10 years before falling to a level close to 1 (Table Vc). The estimated risks associated with these interactions were not affected when the other covariates were taken into account (Table IV); neither were they

TABLE III – ESTIMATED ORs[1] FOR BLADDER CANCER ACCORDING TO TIME-RELATED PARAMETERS

	Cases	Controls	OR	CI (95%)	*p*-value[2]
Total duration of cigarette consumption (yr)					
Non-smokers	35	104	1.00		***
1–9	19	34	1.78	[0.88–3.62]	
10–19	29	45	1.87	[1.00–3.48]	(***)
20–29	64	71	2.81	[1.66–4.77]	
30–39	147	93	5.19	[3.22–8.39]	
40–49	126	80	5.18	[3.16–8.50]	
⩾50	53	30	4.78	[2.56–8.94]	
Total	473	457			
Age at start of smoking (yr)					
Non-smokers	35	104	1.00		***
<17	168	115	4.91	[3.09–7.82]	
18–20	202	158	4.00	[2.57–6.24]	(*)
21–24	47	45	3.51	[1.98–6.37]	
25–30	11	20	1.46	[0.63–3.41]	
>30	10	15	2.04	[0.83–5.04]	
Total	473	457			
Number of years since cessation					
0–2	259	171	1.00		***
3–9	75	54	0.86	[0.57–1.30]	
10–14	36	31	0.69	[0.40–1.18]	
⩾15	68	97	0.38	[0.26–0.57]	
Total	438	353			

[1]OR: odds ratios estimated by logistic regression including matching variables: hospital, age and residence. [2]*p*-value: significance of likelihood ratio χ^2 test; in brackets: significance of likelihood ratio χ^2 after exclusion of non-smokers; CI (95%): 95% confidence interval for OR; NS: Not significant; $^{**}p < 0.01$; $^{***}p < 0.001$.

TABLE IV – BACKWARD STEPWISE LOGISTIC REGRESSION BETWEEN THE OR OF BLADDER CANCER AND TOBACCO-RELATED VARIABLES

	Step 0 Coeff.[1] ± SE[2]	Step 1 Coeff. ± SE	Step 2 Coeff. ± SE	Step 3 Coeff. ± SE
First-order terms				
Average daily consumption (cig./d)				
20–39	−0.45 ± 0.48	−0.46 ± 0.47	−0.47 ± 0.47	−0.50 ± 0.47
≥40	−0.28 ± 0.65	−0.34 ± 0.65	−0.31 ± 0.64	−0.35 ± 0.64
Total duration of consumption (yr)				
20–39	−0.43 ± 0.40	−0.36 ± 0.40	−0.33 ± 0.40	−0.36 ± 0.39
≥40	−0.45 ± 0.51	−0.25 ± 0.48	−0.22 ± 0.48	−0.20 ± 0.47
Inhaling	−0.35 ± 0.44	−0.31 ± 0.44	−0.27 ± 0.43	−0.21 ± 0.42
Black tobacco *vs.* blond or mixed	0.09 ± 0.42	0.11 ± 0.41	0.11 ± 0.41	0.07 ± 0.40
Time since cessation (yr)				
3–9	0.32 ± 0.65	0.39 ± 0.64	0.38 ± 0.64	−0.40 ± 0.58
10–14	−0.99 ± 1.09	−0.87 ± 1.08	−0.88 ± 1.07	−0.53 ± 0.73
≥15	−2.03 ± 0.72	−1.84 ± 0.70	−1.81 ± 0.69	−1.79 ± 0.67
Percentage of filter-tip cigarettes (%)				
50–75	0.56 ± 0.44	0.57 ± 0.43		
75–99	0.09 ± 0.35	0.09 ± 0.35		
100	−0.09 ± 0.23	−0.09 ± 0.23		
Age at start (yr)				
18–20	−0.14 ± 0.20			
21–24	−0.07 ± 0.31			
25–30	−0.68 ± 0.47			
≥31	−0.54 ± 0.57			
Matching variables (age, hospital, residence)				
Interaction terms				
Total duration of consumption × average daily consumption				
(20–39 yr) × (20–39 c/d)	1.00 ± 0.54	0.99 ± 0.53	1.01 ± 0.53	1.06 ± 0.52
(20–39 yr) × (≥40 c/d)	1.40 ± 0.78	1.48 ± 0.78	1.43 ± 0.77	1.53 ± 0.76
(≥40 yr) × (20–39 c/d)	0.33 ± 0.56	0.37 ± 0.55	0.38 ± 0.55	0.38 ± 0.54
(≥40 yr) × (≥40 c/d)	1.59 ± 0.95	1.70 ± 0.94	1.63 ± 0.94	1.66 ± 0.94
Inhaling × black tobacco	1.13 ± 0.47	1.14 ± 0.47	1.10 ± 0.47	1.14 ± 0.46
Type of tobacco × time since cessation				
black × 3–9	−0.83 ± 0.63	−0.89 ± 0.63	−0.89 ± 0.63	−0.88 ± 0.63
black × 10–14	−1.17 ± 0.82	−1.28 ± 0.81	−1.22 ± 0.81	−1.36 ± 0.79
black × ≥15	1.09 ± 0.67	1.05 ± 0.66	1.03 ± 0.67	1.03 ± 0.66
Inhaling × time since cessation				
inh. × 3–9	0.01 ± 0.48	0.05 ± 0.48	0.02 ± 0.48	
inh. × 10–14	1.62 ± 0.89	1.63 ± 0.88	1.61 ± 0.88	
inh. × ≥15	−0.01 ± 0.46	−0.06 ± 0.45	−0.04 ± 0.45	

[1]Coeff: estimated regression coefficient.–[2]SE: standard error of the estimate.

TABLE VA – ODDS RATIOS FOR BLADDER CANCER ACCORDING TO AVERAGE DAILY CIGARETTE CONSUMPTION, ESTIMATED FOR EACH CATEGORY OF DURATION OF SMOKING (ADJUSTED FOR AGE AT DIAGNOSIS)

Average daily consumption (cig./day)	Total duration of cigarettes consumption (yr)								
	1–20			21–40			≥41		
	OR	CI[1] (95%)	Cas./cont.	OR	CI (95%)	Cas./cont.	OR	CI (95%)	Cas./cont.
1–19	1.00		26/40	1.00		83/91	1.00		91/60
20–39	0.87	(0.32–2.02)	16/28	1.68	(1.08–2.60)	98/62	0.98	(0.62–1.67)	72/47
≥40	0.78	(0.25–2.46)	6/11	3.00	(1.41–6.45)	30/11	3.52	(0.97–12.8)	16/3

[1]CI (95%): 95% confidence interval for odds ratio (OR).

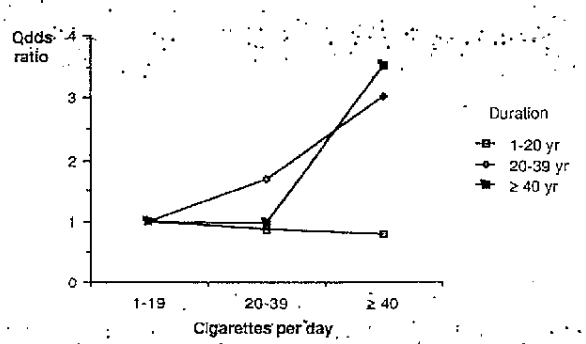

FIGURE 1 – Odds ratio of bladder cancer according to daily cigarette consumption (Table VA).

modified by adjustment for the incident or non-incident status of cases.

The use of the conditional logistic regression model induced only minor changes in the odds ratio estimates.

No occupational exposure was found to be either a confounder or an effect modifier for the association between tobacco-related variables and bladder cancer.

DISCUSSION

Our study confirms the causal role of cigarette consumption in bladder cancer, and provides further information about the effects of inhalation and of type of tobacco smoked.

In our analysis, we excluded the pairs whose controls had

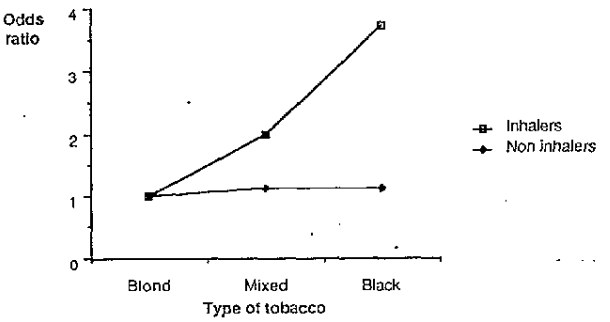

FIGURE 2 – Odds ratio of bladder cancer according to type of tobacco (Table VB).

been admitted for ischemic heart or vascular disease. It might be wondered whether this could cause underestimation of the proportion of smokers in the control group, and therefore overestimation of the relationship between smoking and bladder cancer. Since the controls were selected from hospital departments, their distribution according to cause of hospitalization only reflected the size of these departments, but not the distribution of these diseases among the general population. It may be reasonably assumed that heart and vascular diseases were well represented in all the controls, whatever the reason for their admission to hospital. In agreement with Pearce and Checkoway (1988), we concluded that exclusion of the pairs whose controls had been admitted for ischemic heart or vascular disease was advisable, to reduce selection bias without introducing an overestimation of relative risk. Another bias could have arisen from the fact that some cases were incident and others were not. However, our estimates did not seem to be affected when the incident or non-incident nature of the cases was taken into account, and their heterogeneous recruitment could at most have led to dilution of the risk measurements. Lastly, no other risk factor appeared to be a confounder for smoking variables. These different points substantiate the validity of our data.

In our study, the age-adjusted OR for all smokers *vs.* non-smokers was assessed at about 4, *i.e.*, higher than in studies conducted in Britain (Doll and Peto, 1976; Carwright *et al.*, 1983; Morrison *et al.*, 1984), and the USA (Hammond and Horn, 1958; Cole *et al.*, 1971; Morrison *et al.*, 1984; Najem *et al.*, 1982; Hartge *et al.*, 1987); it was a little lower than the risks reported in Italy (Vineis *et al.*, 1984) and Argentina (Iscovich *et al.*, 1987). Relative risks observed in Denmark, where black tobacco has been traditionally smoked, vary from 1.9 (Mommsen *et al.*, 1983) to 3.6 (Møller-Jensen *et al.*, 1983). In agreement with most other investigators, we found a clear relationship between average daily consumption and bladder cancer risk, a strong relationship between total duration of smoking and bladder cancer, and a clear regular decrease in the odds ratio with time since cessation of smoking.

On the other hand, our study indicates that average daily consumption and OR for bladder cancer were only related when total duration of smoking exceeded 20 years. As stated above, the colinearities between time-related variables required great caution to be exercised when interpreting these results. However, our results suggest that a given latency period is necessary for tumor development, so that the dose-effect relation (*i.e.*, relation between average daily consumption and bladder cancer risk), is only revealed when duration of consumption exceeds this period.

The OR was about twice as high for smokers who inhaled as for those who did not, as already reported in France by Schwartz *et al.* (1961). The OR was also about twice as high for smokers of black as of blond tobacco, confirming the results of Vineis *et al.* (1984) and Iscovich *et al.* (1987).

Moreover, there was a significant interaction between inhaling and type of tobacco, and the excess risk of black tobacco consumption was only found among inhalers. It might reflect the modifying effect of inhaling on the metabolism of some cigarette components—possibly nitrosamines—whose concentration is higher in black than in blond tobacco (Estève *et al.*, 1984).

Results concerning time parameters can be compared to the predictions provided by the multistage models of carcinogenesis. As explained by Breslow and Day (1987), these models are able to predict how relative risks may evolve with the time parameters, depending on whether the early or late stage of carcinogenesis is mainly affected by a given exposure. In short, when exposure involves late-stage agents, the relative risk is independent of age at the start of exposure and drops rapidly after exposure stops. For exposure to an early-stage agent, the younger the age at the start of exposure, the higher the relative risk; after cessation, the relative risk still increases for a time and then remains constant.

In our study, the problems involved in assessing the effect of

TABLE VB – ODDS RATIOS FOR BLADDER CANCER ACCORDING TO TYPE OF TOBACCO, ESTIMATED FOR INHALERS AND NON-INHALERS (ADJUSTED FOR AGE AT DIAGNOSIS)

Type of tobacco	Non-inhalers			Inhalers		
	OR	CI[1] (95%)	Cas./cont.	OR	CI (95%)	Cas./cont.
Blond	1.00		14/22	1.00		10/18
Mixed	1.13	(0.37–3.55)	8/12	1.98	(0.74–5.30)	22/21
Black	1.12	(0.54–2.32)	86/118	3.73	(1.67–8.36)	267/134

[1]CI (95%): 95% confidence interval for odds ratio (OR).

TABLE VC – ODDS RATIOS FOR BLADDER CANCER ACCORDING TO TIME SINCE CESSATION OF SMOKING ESTIMATED FOR EACH TYPE OF TOBACCO (ADJUSTED FOR AGE AT DIAGNOSIS)— REFERENCE CATEGORY: NON-SMOKERS

Years since cessation	Blond or mixed tobacco smokers			Black tobacco smokers		
	OR	CI[1] (95%)	Cas./cont.	OR	CI (95%)	Cas./cont.
0–2	3.36	(1.78–6.35)	32/39	6.63	(4.26–10.31)	210/115
3–9	6.37	(2.21–18.38)	11/7	4.49	(2.62–7.68)	59/45
10–14	6.87	(1.82–25.91)	7/4	3.47	(1.78–6.75)	26/25
⩾15	0.52	(0.17–1.59)	4/23	2.63	(1.58–4.37)	58/67

[1]CI (95%): 95% confidence interval for odds ratio (OR).

age at the start of smoking were caused not only by colinearities but also by the confounding effect of inhalation. The evolution of the OR after cessation of smoking differed according to the type of tobacco. Although, in smokers of both black and blond tobacco, the level of risk had clearly diminished 15 years after cessation, the drop in the odds ratio was immediate in smokers of black tobacco but delayed in those of blond tobacco. The unstable nature of the estimates due to the small number of smokers of blond tobacco might not be sufficient to explain this difference. Vineis *et al.* (1988) did not indicate such a lag, but former smokers of blond tobacco were all considered together in this study, regardless of the number of years since cessation. Among smokers of black tobacco, the way in which the odds ratio decreased after cessation of smoking is evocative of a mainly late-stage intervention, but the persistence of an elevated risk after 15 years also suggests an early-stage action. The observed pattern is quite similar to the finding of Vineis *et al.* (1988). In contrast, among smokers of blond tobacco, the rise observed after cessation mainly evokes the involvement of early-stage agents.

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